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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,285	01/15/2001	Nicholas C. Nicolaides	MOR-0017	2664

7590 07/13/2004

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,285	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-83* is/are pending in the application.

4a) Of the above claim(s) *14-21,25,30-67,69 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13,22-24,26-29,68,70 and 72-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim 1 has been amended, and claim 83 has been added by the amendment dated 4/22/2004.

Applicant's comments regarding the withdrawal of claim 22 from examination is correct, and thus, claim 22 has been rejoined for examination. In view of the amendment to claim 1, withdrawn claim 21, which is dependent from claim 1, does not appear to be a correct dependent claim. Clarification is requested. Also, claim 26 has been rejoined for examination.

Claims 14-21, 25, 30-67, 69, 71 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Elected claims 1, 4-13, 22-24, 26-29, 68, 70, 72-83 readable on the elected invention are pending for examination.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-13 are rejected under 35 USC 102(b) as being anticipated by, on the alternative, under 35 USC 103 as being unpatentable over Cerniglia (Appli. Environ. Microbiol. 56, 3, 661-668, 1990) or LaVoie, Carcinogenesis, Vol. 6, pp. 1483-1488, 1985

The claims are readable on yeast cells or fungal cells. Cerniglia *et al.* teaches a method of administering 9, 10-dimethylanthracene as a carbon source for the growth of the fungus *Cuuninghamella elegans* ATCC 36112.

LaVoie teaches a method of administering a suitable or effective amount of numerous methylated anthracenes, *e.g.,* 1-, 2-, 99-, 2,9- and 9,10-demethylanthracene 9, as a carbon source for inducing tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes in a yeast organism, *S. typhimurium* TA 98 and TA100. Since the yeast organism contains a singular cell, the limitation "*in vitro*" is embraced by method steps employed in LaVoie.

Given the method steps and materials disclosed in Cerniglia *et al.* and LaVoie are identical to that of the claims, the method of Cerniglia *et al.* would necessarily exhibit the biological function intended for 9, 10-dimethylanthracene.

With respect to an elected anthracene for examination, it would also have been obvious for of ordinary skill in the art to as a matter of design choice or minor modifications to employ any known anthracene including those elected anthracenes as claimed in the assay employed in in the cited prior art. One of ordinary skill in the art would have been motivated to employ any known anthracene or a combination of anthracene compounds or known mutagenic compounds simply because of its equivalent effect or combination effect, respectively, in generating a mutation in a treated yeast cell.

Claims 1, 4-13, 22, 23, 26, 68, 72-83 are rejected under 35 USC 103, as being unpatentable over Euler (Caplus Database, AN: 1948:32360, abstract only).

The claims are readable on an assay of detecting a phenotype on plant seeds exposed to anthracene or a combination of anthracenes and additional anthracene or other mutagens, wherein the detected phenotype is a result of a mutation of a gene in the seed.

Euler teaches that a number of genotoxic compounds such as camphor, anthracene, and benzoquinone are effective for introducing a mutation in an endogenous gene contained in pollens, and in plants treated with these compounds, no ears of grain were developed.

With respect to an elected anthracene for examination, it would also have been obvious for of ordinary skill in the art to as a matter of design choice or minor modifications to employ any known anthracene including those elected anthracenes as claimed in the assay employed in Euler. One of ordinary skill in the art would have been motivated to employ any known anthracene or a combination of anthracene compounds or known mutagenic compounds simply because of its equivalent effect or combination effect, respectively, in generating a diminished catalase activity in treated plants.

Thus, the claimed invention was *prima facie* obvious.

Claims 23, 68, 70 are rejected under 35 USC 103 as being unpatentable over unpatentable over Euler (Caplus Database, AN: 1948:32360, abstract only) taken with

Kimm (Korean J. of Biochemistry, 1982, Vol. 14, No. 1, pp. 1-8, abstract), and Laduca, Diss, Abstr Int [B], 55, 11, 4741, 1995, Database CancerLit.

To the extent that Euler does not teach an administration of additional environmental caricinogens such as MNNG and NMU, Kimm teaches that these environmental carcignogens are effective for generating a mutation in vegetables. Thus, it would have been obvious for one of ordinary skill in the art to employ an additional mutagen such as MMNG or NMU in the method of Euler as a matter of increasing a combination effect and reducing the time needed for a mutation or mutational phenotype to occur. One would have expected such since Euler teaches that plants treated with a mutagenic chemical compound all produce no ears of grains.

Thus, the claimed invention was *prima facie* obvious.

Claims 23-24, 26-29 are rejected under 35 USC 103(a) as being unpatentable over any of LaVoie, Carcinogenesis, Vol. 6, pp. 1483-1488, 1985, taken with any of Krahn, Wigley and Slaga, and further in view of Chakravarti *et al.* (PNAS, Vol. 92, pp. 10422-10426, 1995).

LaVoie teaches a method of administering an suitable or effective amount of numerous methylated anthracenes, *e.g.,* 1-, 2-, 99-, 2,9- and 9,10-demethylanthracene 9, as a carbon source for inducing tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes in an organism, *S. typhimurium* TA 98 and TA100. LaVoie also reviews the art of employing methylated anthracenes as a

mutagene and teaches that on the basis oh his study, wherein a different dose of methylated anthracenes was employed, the tumor-innitiating activity of methylated anthracenes can be initiated on mouse skin (Tables I and II, page 1485, column 2, p. 1487, column 1 bridging column 2.

LaVoie does not teach the method done in an *in vitro* or cultured animal cell such as hepatocytes and Chinises hamster cells. However, such methods of using an anthracene or any well known mutagen is well-established in the prior art, as evidenced by the full disclosures of the cited Machala, Krahn, Wigley, Slaga, and Hubbbard.

It would have been obvious for of ordinary skill in the art to as a matter of design choice or minor modifications to employ any known anthracene including those elected anthracenes as taught in LaVoie in any in vitro or cultured animal cell. One of ordinary skill in the art would have been motivated to do so because the prior art, as exemplified by Machala, Krahn, Wigley, Slaga, and Hubbbard, does teach *in vitro* assays of employing well-established mutagens to study or measure the effect of mutation and/or genetoxicity is convention and well-established in the prior art. One would have expected that 1,2-dimethylanthracene would have necessarily produce at least the same effect as demonstrated for other closely related methylated anthracenes employed in LaVoie, particularly since LaVoie teaches that on the basis of his study, wherein a different dose of methylated anthracenes was employed, the tumor-innitiating activity of methylated anthracenes can be initiated on mouse skin and in *S. typhimurium.* Thus, it is already established in the primary reference that tumorigenic activity can generated in mammalian cells exposed to an anthracene. One of ordinary

skill in the art would have a reasonable expectation of success in producing the same effect in mammalian cells in a cultured medium. Moreover, the tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes as shown in LaVoie would necessarily generates a hypermutable cell wherein the presence of methylated anthracenes would necessarily inhibit activities of a mismatch repair in the cell, particularly since LaVoie employs identical method steps and materials as embraced by the claims, and particularly since the as-filed specification teaches that any methylated anthracene as embraced and cited in the claims would exhibit the inhibitory activity against a mismatch repair gene in the cell. As such, and given the fact that *in vitro* assays are convenient and would help to increase sensitivity and reproducibility of the results, particularly since LaVoie teaches that a lower dosage and only a single administration of the amount of anthracene is employed, one of ordinary skill in the art would have been motivated to employ an *in vitro* assay with an increased dosage or amount as employed in any of the other cited prior art so as to ensure and/or enhance the sensitivity and reproducibility of the results and conclusion shown in the primary references.

With respect to the limitation of employing an assay to test whether or not a mutation has occurred in a gene of interest as the result of the effect of a chosen anthracene, wherein the limitation is not taught by LaVoie, Chakravarti teaches that such assays are conventional and routine in the prior art to assay for the effect of gene expression in the presence of an anthracene chosen for the mutation assay, Chakrawati, page 10422, and page 10423.

Thus, it would have been obvious for one of ordinary skill in the art to employ a gene report assay to determine the sensitivity and reproducibility of results due to exposure of tested cells to a chosen anthracene such as 9/10, dimethylanthracene. One of ordinary skill in the art would have been motivated to employ any gene reporter assay known in the prior art in the mutation analysis method employed in the combined cited references because Chakravarti do teach that such assays are conventional and routine in the prior art to assay for the effect of gene expression in the presence of an anthracene chosen for the mutation assay, and because such incorporation of reporter gene expression assays would enhance the sensitivity and reproducibility of results due to exposure of tested cells to a chosen anthracene such as 9/10, dimethylanthracene.

Thus, the claimed invention as a whole, was *prima facie* obvious.

Applicant's arguments (pages 17-19) have been considered by the examiner but are not found persuasive because of the reasons set forth in the stated rejection. Mainly, Applicant argues that none of the prior art, particularly the primary reference, teaches or suggests a step of testing the cell exposed to an anthracene, and that there is not a motivation found in Chakravarti. The arguments are not found persuasive because given the fact that LaVoie teaches that anthracene causes an *in vivo* tumorigenicity, one would have been motivated to employ a step of identifying mutation sin a gene of interest associated with *in vivo* tumorigeniccity. The claims do not necessarily exclude such embodiments, and thus, the claimed remain properly rejected

under 35 USC 103 in view of the combined teachings provided by the totality of the prior art.

Claims 68, 70, 72-82 are now subjected to a prior art rejection. Thus, this action has been made non-final.

Claims 23, 26, 68, 72-83 are rejected under 35 USC 103(a) as being unpatentable over any of Euler (Caplus Database, AN: 1948:32360, abstract only) taken with Zhang (US 20002/0064879 A1).

Euler teaches that a number of genotoxic compounds such as camphor, anthracene, and benzoquinone are effective for introducing a mutation in an endogenous gene contained in pollens, and in plants treated with these compounds, no ears of grain were developed.

With respect to an elected anthracene for examination, it would also have been obvious for of ordinary skill in the art to as a matter of design choice or minor modifications to employ any known anthracene including those elected anthracenes as claimed in the assay employed in Euler. One of ordinary skill in the art would have been motivated to employ any known anthracene or a combination of anthracene compounds or known mutagenic compounds simply because of its equivalent effect or combination effect, respectively, in generating a diminished catalase activity in treated plants. Euler does not teach explicitly that 1,2-dimethylanthracene induces genetoxic hypermutation or tumor induced activity in any cell *in vitro* or *in vivo*.

However, at the time the invention was made, Zhang teaches a method for obtaining a plant with a genetic lesion in a gene sequence flanked in a wild type chromosome by known polynucleotide sequences, comprising exposing the plant and cells thereof to a mutagenic chemical substance. For example, a DNA binding assay was also disclosed in Zhang to determine the presence the mutant gene sequence.

Thus, it would have been obvious for one of ordinary skill in the art to employ a binding assay for detecting the presence of a mutation in a gene(s)in the method of Euler. One would have been motivated to do so because Euler teaches that anthracene is a potent chemical mutagen for inducing random mutation in gene sequence, thereby resulting in a detectable phenotype in a plant or parts thereof, and an mutation assay as disclosed in Zhang would provide one of ordinary skill in the art c convenient tool to analyze the presence of such mutation in a gene sequence contained in the pollens of Euler.

To the extent that the claims are readable on the step of removing the carcinogens and/or mutagens from the medium prior to the analysis step, the claims are also obvious over the cited prior art because one of ordinary skill in the art would have been motivated to do the same in order to monitor the exposing time of carcinogens to the cells.

Thus, the claimed invention was as a whole *prima facie* obvious.

No claim is allowed.

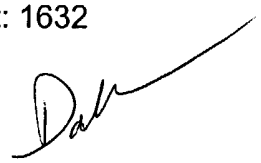
Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632



DAVE T. NGUYEN
PRIMARY EXAMINER